homeostasis. While these tissues move protons, bicarbonate, and other ions transepithelially with a suite of pumps and transporters, how these proton-secreting cells (PSCs) arise developmentally is unknown. Here, we identify a cell type in the *X. laevis* larval that expresses a collection of transporters strikingly similar to those observed in the mammalian kidney, including "kidney"-specific isoforms of the H+V-ATPase and Cl−/HCO3− antiporters related to pendrin and AE1. We show that the transcription factor Foxi1 drives expression, perhaps directly, of some of these genes in a manner similar to the mammalian kidney and epididymis. Moreover, ectopic Foxi1 expression is sufficient to promote the formation of PSC precursors and their intercalation, thus mediating the early specification and morphogenesis of PSCs. We also show that PSCs form in the skin as different subtypes that strongly resemble, in both gene expression and protein localization, the alpha- and beta-intercalated cells of the cortical collecting duct, cells specialized for proton or bicarbonate secretion in the mammalian kidney. Finally, we show that the grainyhead-related transcription factor ubp1L promotes the differentiation of beta-like PSCs and represses alpha-like PSCs. These results hint at a mechanism for PSC specification in vertebrates and shed light on how transport epithelia acquire cellular and functional heterogeneity.

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Program/Abstract # 235
A novel pRb protein network controlling *C. elegans* organogenesis
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Studies on the *C. elegans* Retinoblastoma protein (pRb) ortholog, LIN-35, have uncovered a wide range of cellular and developmental functions that are mechanistically distinct from the canonical role of pRb family proteins in cell cycle control. Correspondingly, mammalian pRb, along with its E2F binding partners, are thought to inhibit tumor progression at a number of distinct steps in addition to their role in repressing cell proliferation. Using a combination of genetic, bioinformatical, and molecular approaches, we have uncovered a novel LIN-35-associated network that regulates development of the *C. elegans* pharynx. More specifically, this pathway controls an early step of pharyngeal morphogenesis that involves stereotypical changes in epithelial cell shape and polarity. Proteins within this network include several conserved ubiquitin-ligase components, a number of transcriptional regulators, and may also involve interactions with the microtubule cytoskeleton. These studies may provide insight into a suggested role for pRb incontrolling cancer metastasis and more generally can shed light on the mechanistic basis for tumor suppression by pRb family members.

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Program/Abstract # 236
Large scale analysis of gene expression in the murine embryonic lung
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In order to obtain a comprehensive framework for understanding and investigating the genetic program that controls mammalian lung development, we have systematically mapped gene expression in the embryonic mouse lung by in situ hybridization. Our analysis of the expression patterns of ~2500 genes has given us insights into the patterning of the lung, the control of the tissue and cell differentiation within the embryonic lung, and numerous molecular markers for those processes. These studies will provide the first global view of the temporal and spatial gene expression program for the formation of the mammalian lung. Many of the genes have specific expression patterns that suggest important and specific roles in embryonic lung morphogenesis. We will demonstrate how these studies focus these subsequent analyses and provide molecular markers to better understand changes to the lung observed in these mutants. We believe these methods can be generalized to study the changes caused by genetic defects, disease, toxins and drugs.

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Program/Abstract # 237
Regulation of airway shape by SPROUTY-mediated control of oriented cell division
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The sizes and shapes of the epithelial tubes that comprise organs such as lung, kidney, and vasculature are critical for their function. Here we investigate the mechanisms that control airway morphogenesis and show that early in lung development, airway shape is a function of the orientation of planar cell division. In normal airways, a large proportion of epithelial cell divisions are oriented parallel to the airway longitudinal axis, whereas this distribution is randomized when RAS-regulated ERK1/2 signaling is increased, leading to shorter and wider airways. We have developed a mathematical model that predicts epithelial tube shape from the distribution of mitotic spindle angles during development, and show that the abnormal shapes of airways in which ERK1/2 signaling is increased can be accounted solely for by the observed alterations in mitotic spindle orientation. Our data reveal that regulating ERK1/2 signaling is essential to ensure appropriate oriented planar cell division, and demonstrate the importance of the negative regulators of this signaling pathway that are encoded by the Sprouty genes for maintaining the normal airway morphogenesis program.

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Program/Abstract # 238
Sprouty gene function in otic placode induction
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Sprouty (Spry) genes encode antagonists of receptor tyrosine kinase signaling, including Fibroblast Growth Factor (FGF) signaling. We have found that in mouse embryos missing both the Spry1 and Spry2 genes ($Spry1^{-/-}$; $Spry2^{-/-}$ double mutants) the otic placode is expanded. Consistent with a role in otic placode induction, we have found that both Spry1 and Spry2 are co-expressed in the pre-otic ectoderm and underlying mesenchyme. FGFs have been shown to induce otic placode formation in multiple species including mouse, chick, and zebrafish. In the mouse, double mutant combinations of Fgf3 and Fgf10 or Fgf8 and Fgf3 result in the absence or dramatic

reduction of the otic placode (Alvarez et al., Dev. 2003, Ladher et al., Genes and Dev. 2005, Wright and Mansour, Dev. 2003, Zelarayan et al., Dev. Bio. 2007). Our observation that the otic placode is expanded in Spry1$^{-/-}$;Spry2$^{-/-}$ double mutants is consistent with the possibility that Spry1 and Spry2 negatively regulate FGF-mediated induction of the otic placode. To test the possibility that Spry1 and Spry2 antagonize FGF signaling during otic placode induction, we have begun genetic interaction experiments between the Spry1, Spry2, and Fgf10 genes. Results from these genetic interaction experiments will be presented.

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Program/Abstract # 239
Canonical Notch signaling is neither necessary nor sufficient for prosensory induction in the mouse cochlea
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The mammalian organ of Corti consists of a highly organized pattern of hair cells and supporting cells that originate from a common population of prosensory progenitor cells. Several signaling pathways including BMP, FGF, SHH and Notch act in concert to achieve this fine grained pattern. The Notch signaling pathway has been well-characterized for its role in regulating differentiation in the organ of Corti through lateral inhibition. Notch signaling from the Jag1 ligand has also been proposed to have a second, earlier role in the specification of sensory progenitors in the inner ear. To examine the role of Notch signaling in these two processes, we conditionally inactivated RBPjk, the transcriptional effector of canonical Notch signaling, throughout the inner ear. We show that in the absence of RBPjk, the cochlear prosensory domain forms normally and hair cells and supporting cells differentiate. However, differentiating hair cells rapidly die in RBPjk mutants. The prosensory domain of the cochlea also differentiates normally in Jag1 conditional mutant mice. Finally, in contrast to the chick basilar papilla, activation of Notch in the mouse cochlea did not induce ectopic sensory patches. Our results indicate that canonical Notch signaling is neither necessary nor sufficient for prosensory specification in the mouse cochlea, suggesting that other signaling pathways are required for the specification of this highly derived sensory organ.

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Program/Abstract # 240
The role of Sox2 in the regulation of eye development
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The basic organization of eye tissues depends on interactions between cephalic ectoderm and optic vesicle. The transcription factor Sox2 plays pivotal roles in the development of both tissues. The Sox2 expression in the pre-placodal cephalic ectoderm is regulated by mainly enhancer N-4, while the same enhancer also participates in Sox2 regulation in the optic vesicle. We have investigated the function of Sox2 in the regulation of eye development, utilizing enhancer N-4 knockout mice. These mice showed the small eye phenotype in adulthood. We examined when this phenotype initiates, and found this traced back to the lens induction stage. The lens placode invagination in enhancer N-4 knockout embryo was delayed at E10.5. The molecular markers of cell differentiation, e.g. crystallins in lens, however, were normally expressed at E13.5, and the morphology of eye was not severely affected except that the sizes of both lens and retina remained smaller than wild type. This observation suggests that the delay of lens placode invagination is causative to the small eye development. An ongoing project is to see whether the ectodermal Sox2 downregulation is sufficient for causing small eyes.

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Program/Abstract # 241
Transcriptome profiling highlights multiple roles for Xrx1 during eye development
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Despite the crucial role played by Xrx1 in controlling eye field specification and maintenance of retinal stem cells multipotency, the genetic program regulated by this transcription factor remains to be largely deciphered. To identify the gene networks controlled by Xrx1, the transcriptome of control Xenopus embryos was compared to that of embryos overexpressing Xrx1 and embryos in which Xrx1 was knocked-down. This analysis, performed using Affymetrix microarrays, detected 44 transcripts displaying a coherent behaviour, i.e., showing increased levels of expression in the gain of function assay and decreased levels in loss of function experiments, or vice versa. In the vast majority of cases, these data have been confirmed by real time PCR and in situ hybridization. The identity of selected transcripts indicates multiple roles for Xrx1 in controlling different phases of retinal specification. These include the regulation of cell movements during eye field formation, the determination of eye field size, the maintenance of a pluripotent cell fate, and the repression of endomesodermal genes. In particular, the latter represents a novel, critical function for a retinal transcription factor, which appears to block, directly or indirectly, endomesodermal signals known to inhibit retinal fate.

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Program/Abstract # 242
pug function is essential for normal limb length
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The radiation of vertebrates to occupy aquatic, terrestrial, and aerial environments involved modifications to the size and shape of their limbs. Limb length is regulated by early signaling centers in the developing limb bud and later by proliferation and outgrowth of the skeletal precursor cells (chondrocytes). Defects in these later stages typically result in shorter, but normally patterned limbs (i.e. dwarfism). Despite recent advances in chondrocyte biology, our understanding of the factors that regulate bone length is incomplete. To expand our knowledge of these factors, we are currently working with a recessive mouse mutant. *pug* mutant limbs appear normal early, but by birth are only ~80% the length of wild-type limbs. Histological analyses revealed